REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIMS STATUS & AMENDMENTS

Claims 1-3 and 5-10 were pending in this application when last examined. These same claims are finally rejected.

Claims 1-3, 6, 9 and 10 have been cancelled without prejudice or disclaimer thereto. Applicants reserve the right to file a continuation or division application on any canceled subject matter.

Upon entry of the present amendment, claims 5 and 7-8 will be pending.

Claim 5 has been amended to better clarify the method steps. Support for this amendment can be found in the specification, for instance, at page 3, lines 1-10, page 5, lines 6-13 and at page 8, line 15 to page 9, line 5.

Attached are a clean copy and a marked-up copy of the substitute specification. The substitute specification corrects minor grammatical and spelling errors too numerous to list. The changes are shown by underlining and lining out. Support for the changes in the substitute specification can be in the original specification. A clean copy of the substitute specification is also attached.

Therefore, no new matter has been added by this amendment.

II. OBJECTION TO THE SPECIFICATION

The specification is again objected to on the basis of a minor informality, such as grammatical and spelling errors. See Office Action, page 1, item 8; page 2, 3rd paragraph.

The attached substitute specification is deemed to overcome this objection.

III. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-3 and 5-10 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite for the reasons set forth at page 2, line 13 to page 3, last line of the Office Action.

The present amendment is deemed to overcome this rejection for the following reasons.

The claims have been amended to better clarify the claimed method steps for measuring PIVKA-II. Specifically, the claims have been amended to recite the specific components of the first and second immunoassay reagents and the contacting step. The claims have also been amended to include a step for measuring PIVKA-II in the test sample. Also, as described in the specification at page 3, lines 6-13, the anti-human prothrombin antibodies also bind PIVKA-II Accordingly, it is clear as to how PIVKA-II is measured. In view of the above, the rejection of claims 1-3 and 5-10 under 35 U.S.C. § 112, second paragraph, is untenable and should be withdrawn.

IV. REJECTION UNDER 35 U.S.C. § 103

Claims 1-3, 9, and 10 are rejected under 35 U.S.C. § 103(a) as obvious over Matsuda in view of Lämmle and Weir, all cited in the previous Office Action. See pages 4-5.

It is respectfully submitted that the present amendment cancelling the rejected claims overcomes this rejection. Nonetheless, Applicants respectfully traverse this rejection as applied to the remaining claims for the following reasons.

Previously, in the response filed December 18, 2003, it was argued that the prior art fails to disclose or suggest the use of anti-PIVKA-II antibodies and antibodies specific for fibrin related substance in a PIVKA-II immunoassay. In reply, the rejection was maintained on the basis that such arguments were directed to limitations not in the claims. See Office Action, page 4, lines 7-9.

Remaining claims 5, 7 and 8 require the use of "anti-PIVKA-II antibodies and antibodies which specifically bind to a human fibrin or a human fibrinogen." Kindly note that claims 5, 7 and 8 were not included in this rejection. Also note that claim also requires the addition of thrombin.

The cited references fail to disclose or suggest the use of antibodies that specifically bind to a human fibrin or a human fibrinogen in an immunoassay for PIVKA-II.

In this regard, Matsuda describes a general enzyme sandwich immunoassay for determination of PIVKA-II utilizing an immobilized anti-PIVKA-II monoclonal antibody. No where does Matsuda disclose or suggest using antibodies which specifically bind to a human fibrin or a human fibrinogen in a PIVKA-II immunoassay. Also, Matsuda fails to disclose the use of thrombin in such an immunoassay (claim 7).

Lämmle generally discloses the structure of PIVKA-II, and prothrombin, which is a thrombin precursor. Lämmle does not teach antibodies which specifically bind to a human fibrin or a human fibrinogen in a PIVKA-II immunoassay. In fact, Lämmle never discusses an immunoassay for PIVKA-II, let alone one involving antibodies that specifically bind to a human fibrin or a human fibrinogen. Nor does Lämmle teach the use of prothrombin or thrombin in an immunoassay (claim 7).

Similarly, Weir never discusses antibodies that specifically bind to a human fibrin or a human fibrinogen, nor immunoassay methods utilizing such. Instead, Weir discloses a method whereby antisera is absorbed with antigens rendered insoluble by covalent binding to an insoluble support such as Sepharose. See Weir, page 12.13, 1st column, last paragraph to 2nd column, first paragraph. Thus, Weir fails to disclose and/or suggest adding antibodies specific to human fibrin or human fibrinogen to an immunoassay to improve the specificity for PIVKA-II.

Weir is also deficient in that it never suggests that the specificity of an immunoassay will be improved by the addition of soluble antigen, such as thrombin, to a reaction sample in an immunoassay. Weir never suggests the addition of soluble antigen, such as thrombin, to a reaction sample in an immunoassay (claim 7).

Furthermore, prior to the claimed invention, PIVKA-II had been measured by immunoassays resulting in poor sensitivity with a low positive rate. Applicants were first to discover that this poor sensitivity was due to unknown reaction substances in the test sample which interfered with the conventional assays. These unknown reaction substances resulted in positive errors in the measurement of PIVKA-II. Applicants further found that this interference was due to the presence of fibrin related substances in the samples.

The instant invention solved this problem in the prior art in that the sensitivity and specificity for PIVKA-II is improved by adding antibodies which specifically bind to a human fibrin or a human fibrinogen to the serum or plasma test sample.

None the cited references discuss the interference problems associated with enzyme immunoassays for PIVKA-II and whether it is attributable to bound or free thrombin in a sample. Nor do the cited references suggest a solution for overcoming this problem.

In sum, the cited references fail to suggest the use of anti-PIVKA-II antibodies specific to the human fibrin or human fibrinogen in an immunoassay for PIVKA-II. The cited references also fail to suggest using thrombin in such immunoassays. As such, the cited references fail to disclose or suggest each and every element of the amended claims.

In view of the above, the rejection of claims 1-3, 9, and 10 under 35 U.S.C. § 103(a) is untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

Motohito KANASHIMA et al.

By: _____
Warren M. Cheek, Jr.
Registration No. 33,367
Attorney for Applicant

WMC/JFW/ksh
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
October 22, 2004

ATTACHMENTS:

1. Substitute specification (Clean and Marked-up Versions).

2. Substitute abstract (Clean and Marked-up Versions).